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PATENT SPECIFICATION (11) 1 602 290

1 602 290

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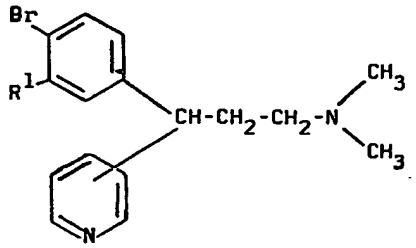
(54) SUBSTITUTED ARALKYL AMINES AND AMINO ARYL ALKENES HAVING THERAPEUTIC ACTIVITY

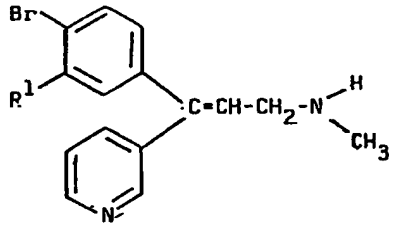
(71) We, ASTRA LÄKEMEDEL AKTIEBOLAG, a Swedish Body Corporate of Strängnäsvägen 44, S—151 85 Södertälje, Sweden, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is related to new compounds of the diarylalkylamine type having therapeutic activity, to methods for preparing such compounds, to pharmaceutical preparations comprising such compounds and to methods of treating non-humans employing such compounds.

British Patent Specification 1,429,068 discloses compounds corresponding to the general formula:

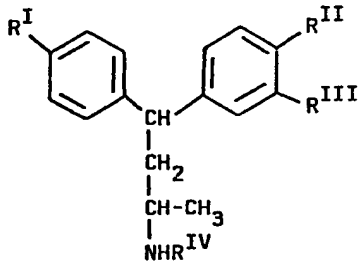


having anti-depressive activity. Belgian Patent Specification 835,802 discloses compounds of the general formula:



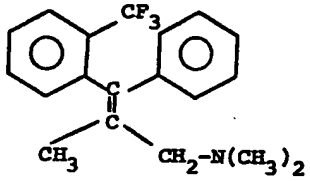
having anti-depressive activity.

Compounds within the general formula



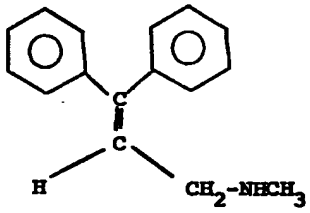
are disclosed by prior publications as follows: $R^I=CH_3O$, $R^{II}=OH$, $R^{III}=R^{IV}=H$ and $R^I=Cl$, $R^{II}=OH$, $R^{III}=CH_3$, $R^{IV}=H$ having hypotensive properties, by British Patent Specification 765,881; $R^I=R^{II}=R^{III}=R^{IV}=H$ by French Patent Specification 2,215,973; $R^I=R^{II}=R^{III}=H$, R^{IV}=tertiary butyl having spasmolytic properties, by British Patent Specification 923,942; and $R^I=R^{II}=R^{III}=H$, $R^{IV}=CH_3$ having spasmolytic properties, by US Patent Specification 2,446,522.

South African Patent Specification 62/4154 discloses i.a. a compound having the formula



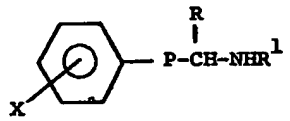
claimed to have a therapeutic utility especially as an anti-tussive.

In J. Med. Chem. *14* 161 (1971) a compound of the formula

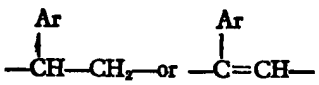


is disclosed as an antidepressant.

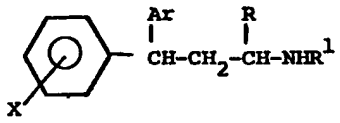
According to the present invention it has been found that compounds of the general formula below have advantageous, therapeutic properties:



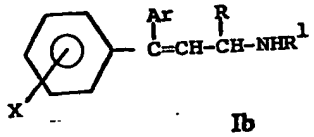
wherein P represents



These compounds may thus b divided into two groups defined by the formulae:

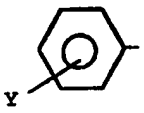


Ia



Ib

In the compounds of formula I Ar represents the group



wherein Y is bound in the 2-, 3- or 4-position and represents a lower alkyl group, a lower alkoxy group, halogen, a trifluoromethyl group, or an amino or a mono- or di-lower alkyl amino group, or Ar represents a pyridyl group bound in the 2-, 3-, or 4-position, X represents hydrogen, a lower alkyl group, a lower alkoxy group, halogen, a trifluoromethyl group, an amino group or a mono- or di-lower alkyl amino group, R is a lower alkyl group and R^1 is hydrogen or a lower alkyl group. By lower alkyl and alkoxy groups are meant groups comprising up to 3 carbon atoms. Halogen may be any of the elements F, Cl, Br or I.

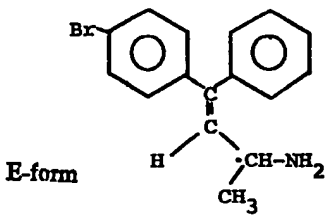
Therapeutically acceptable, anhydrous or hydrated, acid addition salts of these compounds are also within the scope of this invention.

Particularly embodiments of the present invention are the above-defined compounds when in the form of pharmaceutical preparations or when used to treat depression or anxiety. The compounds themselves also represent an embodiment of the invention when X represents hydrogen only, or, when Ar represents pyridyl, x can have any of its defined meanings.

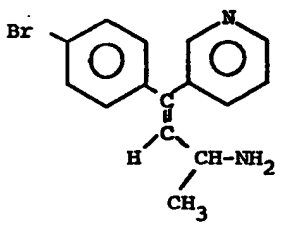
The compounds of formula Ia above contain two asymmetric carbon atoms and can therefore exist in two diastereomeric forms which can be separated by methods known in the art. Further the compounds of formula Ia above may be resolved into their optical enantiomers using optically active acids such as i.a. tartaric acid, mandelic acid and dibenzoyl tartaric acid as known in the art. The compounds of the invention may be used as mixtures of diastereomeric forms or as racemic mixtures of the pure diastereomers or as the pure enantiomers mentioned above. The therapeutic properties may reside to a greater or lesser extent in one of the enantiomers or mixtures mentioned above.

Due to the lack of free rotation in the double bond the compounds of formula Ib may exist in different stereoisomeric forms, that is as cis-trans isomers or, according to the IUPAC nomenclature (J. Org. Chem. *35*, 2849—2867, September, 1970), in an E-form and a Z-form. The compound may be used therapeutically as a mixture of geometrical isomers or in pure E or Z form. The pure geometrical isomers may be prepared from an isomer mixture from an isomer-pure starting material or directly by a stereoselective synthesis.

It should be noted that in the IUPAC nomenclature compounds of formula Ib in the form of pure geometrical isomers which are similar in structure may be named the E-form for one subgroup of compounds and the Z-form for another subgroup. The two structural formulae below illustrate this fact.



E-form

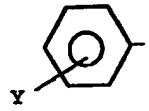


Z-form

All the compounds of formula Ib further contain one asymmetric carbon atom. The compounds of formula Ib may be resolved into their optical enantiomers using optically active acids such as i.a. tartaric acid, mandelic acid, and dibenzoyl tartaric acid as known in the art. The compounds of formula Ib may be used as mixtures especially racemic mixtures, or as the pure enantiomers of the geometrical isomers mentioned above. The therapeutic properties may reside to a greater or lesser extent in one of the enantiomers or mixtures mentioned above.

The compounds of the invention show an activity in the central nervous system which makes them useful as neuropharmacological agents for treatment of various diseases in animals. The compounds are expected to be especially useful as anti-depressive anxiolytic or tranquilizing agents.

Of the compounds of the invention defined by formula I above, those wherein Ar is



are to be specially mentioned, especially those wherein Y is F, Br or CH_3O—.

Preferred individual compounds include:

(β) - 3 - (4 - fluorophenyl) - 1 - methyl - 3 - phenylpropylamine,
(β) - 3 - (4 - bromophenyl) - 1 - methyl - 3 - phenylpropylamine,
(α) - 3 - (4 - methoxyphenyl) - 1 - methyl - 3 - phenylpropylamine, and
(β) - 3 - (3 - bromophenyl) - 1 - methyl - 3 - phenylpropylamine

being non-selective inhibitors of neuronal noradrenaline and 5 - hydroxytryptamine uptake;

(α) - 3 - (2 - bromophenyl) - 1 - methyl - 3 - phenylpropylamine,
(E) - 3 - amino - 1 - (3 - bromophenyl) - 1 - phenylbutene, and
(Z) - 3 - amino - 1 - (3 - bromophenyl) - 1 - phenylbutene

being selective inhibitors of neuronal noradrenaline uptake; and

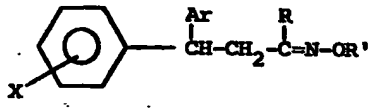
(β) - 3 - (4 - methoxyphenyl) - 1 - methyl - 3 - phenylpropylamine, and
(E) - 3 - amino - 1 - (4 - bromophenyl) - 1 - phenylbutene,

being selective inhibitors of neuronal 5 - hydroxytryptamine uptake; as well as salts of said compounds. The neuronal uptake mechanisms are discussed further in the section " Pharmacological evaluation " below.

Generally preferred in all classes of the compounds of the invention are those wherein R^1 represents hydrogen and R represents a methyl group.

The compounds of the invention of formula Ia may be prepared by

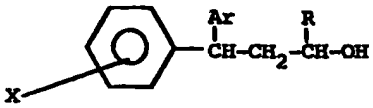
a) reducing a compound of the formula



II

wherein Ar, X and R are as defined above and R' is a hydrogen atom or an alkyl, acyl or alkylsulfonyl group having 1—3 carbon atoms, to obtain a compound of formula Ia in which R^1 is hydrogen, and if desired converting this primary amine to a secondary amine in a manner known in the art, e.g. to the corresponding methylamine by methylation. The reduction may be carried out by known methods e.g. employing a hydride reagent such as lithium aluminium hydride.

b) preparing a reactive ester of an alcohol of the formula

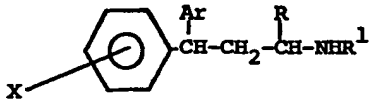


III

wherein Ar, X and R are as defined above, and reacting the ester obtained with an amine of the formula NH_2R^1, wherein R^1 is as defined above. The reactive ester may

be obtained by treating the alcohol with a halogenating agent such as thionyl chloride, thionyl bromide or phosphorus tribromide, or with an arylsulphonyl halide such as *p*-toluenesulphonyl chloride,

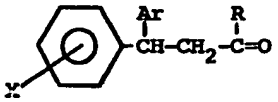
c) reducing a compound of the formula



Ib

wherein Ar, X, R and R^1 are as defined above. The reduction may be carried out by methods known in the art e.g. by catalytical hydrogenation using catalysts such as Raney nickel, palladium on charcoal, platinum dioxide or rhodium,

or d) reacting a ketone of the formula



IV

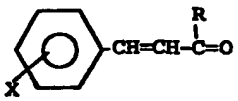
wherein Ar, X and R are as defined above, with ammoniumformate or methylammoniumformate according to Leuckart-Wallach to obtain a compound of formula Ia in which R^1 is hydrogen or methyl. The formate may be added as such, or obtained by formation *in situ* from formamide or methyl formamide, or from formic acid and ammonia or methylamine.

The intermediates of formulae II, III, and IV above are novel.

The intermediates of formula I may be prepared by reacting the ketone of the formula IV above with a hydroxylamine derivative of formula NH_2OR', wherein R' is as defined above.

The intermediates of formula III may be prepared by hydride reduction of the compound of formula IV which, in turn, may be obtained by

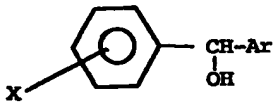
1) reacting an alpha, beta-unsaturated ketone of the formula



V

wherein X and R are as defined above, with a metal-organic reagent such as magnesium, lithium or sodium derivative of an arylhalide of the formula Ar—Y', wherein Ar has the meaning defined above and Y' is a chlorine, bromine or iodine atom, in the presence of catalytic amounts of cuprous ions,

2) reacting a diarylcarbinol of the formula



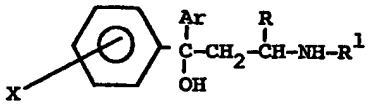
VI

wherein Ar and X are as defined above, first with thionyl chloride, then with ethyl acetoacetate in the presence of a suitable condensation catalyst such as sodium acetate.

The compounds of formula Ia are preferably prepared by method a). The reaction according to method a) is preferably performed in diethyl ether with a slight excess of lithium aluminium hydride under inert atmosphere.

The new compounds of formula Ia may be used therapeutically as the racemic mixtures of [+]- and [−]-forms, which are usually obtained by the synthesis. Isomer mixtures obtained may be resolved by methods known *per se* into the corresponding optically active isomers. If desired, the optically active isomers may be prepared by way of direct synthesis, e.g. *via* an optically active compound as described above.

The compounds of the invention of formula Ib may be prepared by:
e) Dehydration of a carbinol f the formula

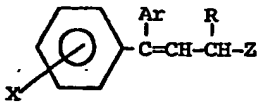


VII

wherein Ar, X, R and R^1 are as defined above.

The dehydration of the starting material may be effected by treatment with hydrochloric acid HCl and heating of the reacting mixture. The dehydration of the starting material may also be effected by means of other types of acid-catalysis, such as by means of sulfuric acid H_2SO_4, phosphoric acid H_3PO_4, potassium hydrogen sulphate $KHSO_4$, or oxalic acid $(CCOH)_2$. Other methods for the dehydration of the starting material to form a compound of the formula I are dehydration using phosphous oxychloride $POCl_3$ in pyridine, and dehydration with thionylchloride, $SOCl_2$, in pyridine. Also a catalytic dehydration of the starting material may be used. The dehydration is in this case carried out at a temperature of 300 to 500° C using a catalyst such as kaolin, alumina or aluminium oxide.

f) Reaction of a compound of the formula

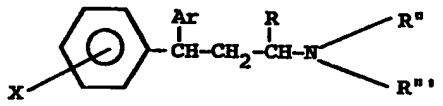


VIII

wherein Z is a leaving group such as F, Cl, Br, I or OSO_2R^2, wherein R^2 is alkyl, aralkyl or aryl, with an amine of the formula HN_2R^1 or with a derivative thereof such as hexamethylenetetraamine, alkyliphthalimide, lithium bisbenzenesulfeneamide, guanidine, sodium cyanate, sodium azide, a carboxamide or a sulfonamide. When a derivative of NH_2R^1 is used, the product obtained is subsequently hydrolyzed or in some other way converted into a primary or secondary amine of formula Ib. A preferred amine derivative is potassium phthalimide.

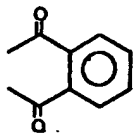
This reaction is also useful for preparation of the compounds of formula Ia by employing as a starting material a saturated compound corresponding to the compound of formula VIII.

g) Oxidation (halogenation) of the benzylic carbon atom of a compound of formula IX.

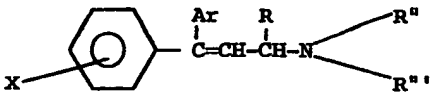


X

e.g. with N-bromosuccinimide, R″, R‴ being protecting groups for the amino function preferably joined as the group



or alternatively the group —N—(R″)—(R‴) being derived from one of the amine derivatives specified under f) above, followed by elimination of the group formed by oxidation at the benzyl carbon atom, to provide a compound of the formula

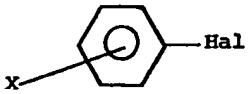


X

which is transformed into the compound of formula Ib wherein R^1 is hydrogen by removing groups R″ and R‴, e.g. by hydrolysis or hydrazinolysis. In this manner it is possible to synthesize the compounds of formula Ib from the corresponding saturated compounds of formula Ia, by introducing in those compounds protecting groups R″ and R‴ in a known manner to obtain a compound of formula IX.

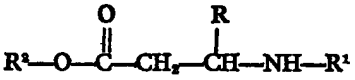
The intermediates of formulae VII, VIII, IX and X above are novel.

The intermediates of formula VII may be obtained by preparing a Grignard or lithium compound from a halobenzene of the formula



Hal=Br, Cl

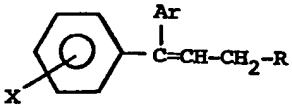
and reacting it with an ester of the formula



wherein R^2 is an alkyl, aralkyl or aryl group.

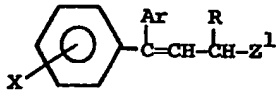
The intermediate of formula VII may be isolated (cf. Example 15) and subsequently dehydrated or alternatively the crude product in the preparation of formula VII may be dehydrated directly (cf Example 17).

The intermediate of formula VIII may be obtained from a compound of formula



XI

wherein Ar and R are as defined above, by oxidation of the allylic carbon to form a compound of formula



VIIA

wherein Z^1 represents Z or OH, e.g. by reaction with N-bromosuccinimide (Z^1=Br) or selenium dioxide (Z^1=OH). The latter compound may be transformed to a reactive derivative VIII by treatment with an agent such as $SOCl_2$, $SOBr_2$ or PBr_3 or with $ClSO_2R^1$.

Any primary amine formed by the above processes may be converted to a secondary amine as indicated for process a), and the free base may be converted to an anhydrous or hydrated, acid addition salt.

In clinical practice the compounds of the present invention will normally be administered orally, rectally or by injection, in the form of pharmaceutical preparations comprising the active ingredient either as a free base or as a pharmaceutically acceptable acid addition salt, e.g. the hydrochloride, hydrobromide, lactate, acetate, phosphate, sulphate, sulphamate, citrate, tartrate or oxalate in association with a pharmaceutically acceptable carrier. Accordingly, terms relating to the novel compounds of this invention whether generically or specifically are intended to include both the free amine base and the acid addition salts of the free base, unless the context in which

such terms are used, e.g. in the specific Examples would be inconsistent with the broad concept. The carrier may be a solid, semi-solid or liquid diluent or capsule. These pharmaceutical preparations constitute a further aspect of this invention. Usually the active substance will constitute from 0.1 to 99% by weight of the preparation, more specifically from 0.5 to 20% by weight for preparations intended for injection and from 2 to 50% by weight for preparations suitable for oral administration.

The produce pharmaceutical preparations containing a compound of the invention in the form of dosage units for oral application the selected compound may be mixed with a solid pulverulent carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches, such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, and polyethylene glycol waxes, and then compressed to form tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, e.g. gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet can be coated with a lacquer dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different active substances or different amounts of the active compounds.

For the preparation of soft gelatine capsules (pear-shaped closed capsules) consisting of gelatine and for example, glycerol or similar closed capsules, the active substance may be mixed with a vegetable oil. Hard gelatine capsules may contain granulates of the active substance in combination with solid, pulverulent carriers such as lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatine.

Dosage units for rectal application can be prepared in the form of suppositories comprising the active substance mixed with a neutral fatty base, or gelatine rectal capsules comprising the active substance mixed with vegetable oil or paraffin oil.

Liquid preparations for oral applications may be in the form of syrups or suspensions, for example, solutions containing from 0.2% to 20% by weight of the active substance herein described the balance being sugar and a mixture of ethanol, water, glycerol, and propyleneglycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccarine and carboxymethyl-cellulose as a thickening agent.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance preferably in a concentration of from 0.5% to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

Suitable daily doses of the compounds of the invention in therapeutic treatment is 25 to 250 mg for peroral administration, preferably 50 to 150 mg, and 5 to 50 mg for parenteral administration preferably 10 to 30 mg. A preparation in dosage unit form for oral administration may contain 10 to 50 mg, preferably 10 to 25 mg of active substance per dosage unit.

The present invention will now be described by the following Examples, some of which describe preparation of intermediates. Examples 12 to 19 describe the preparation of compounds which may be present in the preparations of the invention.

Example 1.

Preparation of 4 - (3 - bromophenyl) - 4 - phenylbutan - 2 - one.

To 2.4 g (0.10 mol) of magnesium turnings, covered with 20 ml of anhydrous diethyl ether and treated with some crystals of iodine under nitrogen atmosphere, 23.5 g (0.10 mol) of 1.3 - dibromobenzene in 80 ml of ether was added. The rate of addition was adjusted, to maintain a gentle reflux of the solvent. When the Mg turnings had disappeared (30 min) 0.75 g (0.005 mol) of cuprous bromide was added and the mixture was stirred for 10 min at room temperature. A solution of 13.6 g (0.09 mol) of benzylactone in 100 ml of ether was added dropwise at +10° C. Then the reaction mixture was allowed to reach room temperature for 2 h. The mixture was poured into 400 ml of a 10% aqueous solution of ammonium chloride, the aqueous layer was separated and the product was extracted with 2 × 200 ml of ether. The ethereal layer was washed with water, dried with Na_2SO_4 and the solvent was evaporated. The crude 4 - (3 - bromophenyl) - 4 - phenylbutan - 2 - one obtained (26.5 g, 0.086 mol) was added to a solution of 20 g (0.28 mol) of hydroxylamine hydrochloride in 300 ml of ethanol and 100 ml of anhydrous pyridine. The mixture was heated under reflux for 4 h. After cooling the solvent was evaporated *in vacuo* and the ketoxime

was extracted with ether from an aqueous solution. Washing of the extract with water and drying followed by evaporation of the solvent gave 27.5 g of 4 - (3 - bromophenyl) - 4 - phenylbutan - 2 - one oxime.

Example 2.

Preparation of 3 - (3 - bromophenyl) - 1 - methyl - 3 - phenyl - propylamine oxalate. (Method a).

To the oxime obtained according to Example 1 (27.5 g) 100 ml of carbon tetrachloride was added and evaporated twice in order to remove traces of water. The residue was dissolved in a mixture of 300 ml of anhydrous ether and 150 ml of anhydrous tetrahydrofuran. To the stirred mixture 3.5 g (0.0086 mol) of lithium aluminum hydride was added in portions under nitrogen atmosphere at room temperature. The reaction mixture was stirred for 8 h. Then 25 ml of 2 M NaOH was dropwise added and the precipitated inorganic salts were removed by filtration. The filtrate was shaken with 3 × 300 ml of 1 M HCl and the combined aqueous layers were made alkaline by addition of 35 ml of 30% NaOH. Extraction with 3 × 200 ml of methylene chloride, washing, drying and evaporation of the solvent gave 8.9 g of the primary amine as an oil. To a hot solution of 7.9 g (0.026 mol) of the amine in 100 ml of isopropylalcohol 1.1 g (0.014 mol) of oxalic acid in 10 ml of ethanol was added. 6.2 g of the diamine oxalate was collected. Recrystallization from 160 ml of a mixture of ethanol and isopropylalcohol (1:1) yielded 4.43 g, mp 134—138° C.

Analysis: C calcd 58.5%, found 58.7%, H calcd 5.48%, found 5.80%, N calcd 4.01%, found 4.07%.

Example 3.

Separation of 3 - (3 - bromophenyl) - 1 - methyl - 3 - phenylpropylamine into its diastereomers.

The free amine (2.9 g, 0.009 mol) obtained from 3.8 g of the oxalate prepared according to Example 2, was dissolved in 40 ml of ethyl acetate. A hot solution of 1.1 g (0.009 mol) of maleic acid in 20 ml of ethanol was added. There was obtained 1.3 g of the maleate. Recrystallization from 18 ml of isopropylalcohol gave 0.65 g of the pure alpha isomer, mp 163—165° C. The high field part of the NMR spectrum ($COCl_3$) displayed a triplet at 4.1 ppm (J=7.8 Hz), a quartet at 2.8 ppm (J=6.2 Hz), a double doublet at 2.0 ppm (two protons) and a doublet at 1.5 ppm (J=6.1 Hz) (three protons).

Analysis: C calcd 57.15%, found 57.45%, H calcd 5.28%, found 5.35%, Br calcd 19.01%, found 19.05%, N calcd 3.33%, found 3.20%, O calcd 15.23%, found 15.00%.

The solvents of the first mother liquors of the diamine oxalate prepared according to Example 2 were evaporated and the residue was extracted with ether from an alkaline solution. There was obtained 1.2 g of free amine. The fumarate was prepared in ethyl acetate from half an equivalent of fumaric acid and recrystallized twice from acetonitrile-isopropylalcohol affording 0.28 g of the pure beta isomer as the diamine fumarate, mp 184—186° C.

Analysis: C calcd 59.7%, found 60.3%, H calcd 5.6%, found 5.7%, N calcd 3.9%, found 3.7%.

Example 4.

(α) - 3 - (4 -fluorophenyl) - 1 - methyl - 3 - phenylpropylamine oxalate, mp 186—188° C (EtOH—EtOAc, 1:1) and (β) - 3 - (4 - fluorophenyl) - 1 - methyl-3 - phenylpropylamine hydrochloride, mp 171—172° C (EtOAc) were prepared from 4 - (3 - fluorophenyl) - 4 - phenylbutan - 2 - one oxime in accordance with Examples 2 and 3.

Example 5.

(α) - 3 - (4 - bromophenyl) - 1 - methyl - 3 - phenylpropylamine maleate, mp 168—170° C (EtOH—EtOAc, 1:1) and (β) - 3 - (4 - bromophenyl) - 1 - methyl-3 - phenylpropylamine maleate, mp 161—162° C (i-PrOH—EtOAc, 3:1) were prepared from 4 - (4 - bromophenyl) - 4 - phenylbutan - 2 - one oxime in accordance with Examples 2 and 3.

Example 6.

(α) - 3 - (4 - methoxyphenyl) - 1 - methyl - 3 - phenylpropylamine maleate, mp 146—148° C (i-PrOH) and (β) - 3 - (4 - methoxyphenyl) - 1 - methyl - 3-

phenylpropylamine maleate, mp 124—133° C (EtOAc) were prepared from 4 - (4-methoxyphenyl) - 4 - phenylbutan - 2 - one oxime in accordance with Examples 2 and 3.

Example 7.

(α) - 1 - methyl - 3 - (4 - trifluoromethylphenyl) - 3 - phenylpropylamine maleate, mp 165—166° C. and (β) - 1 - methyl - 3 - (4 - trifluoromethylphenyl)-3 - phenylpropylamine maleate, mp 165—167° C. were prepared from 4 - (4 - trifluoromethylphenyl) - 4 - phenylbutan - 2 - one oxime in accordance with Examples 2 and 3.

Example 8.

Preparation of 4 - (2 - bromophenyl) - 4 - phenylbutan - 2 - one.

To a solution of 24.3 g (0.13 mol) of 2 - bromobenzaldehyde in 80 ml of acetone, 1.0 ml of 10 M NaOH was slowly added at 0° C. The reaction mixture was allowed to reach room temperature and stirred for another 2 h. Then it was poured into 400 ml of water, to which 10 ml of 2 M HCl had been added. Extraction with ether, drying and evaporation of the solvent gave 18.9 g of 2 - bromobenzylacetone as an oil. This was dissolved in 150 ml of ether and added to a Grignard reagent prepared from 1,1 g (0.045 mol) of magnesium turnings 6.6 g (0.042 mol) of bromobenzene and 0.2 g of CuBr in 150 ml of ether. The mixture was stirred under nitrogen atmosphere for 2 h. It was poured into 450 ml of ice-water to which 18 g of ammonium chloride had been added. Extraction with ether gave 11.0 g of the desired ketone as an oil.

Example 9.

(α - 3 - (2 - bromophenyl) - 1 - methyl - 3 - phenylpropylamine maleate, mp 145—146° C (i-PrOH) and (β) - 3 - (2 - bromophenyl) - 1 - methyl - 3 - phenylpropylamine maleate, mp 135—137° C (EtOH—EtOAc, 1:4) were prepared from 4 - (2 - bromophenyl) - 4 - phenylbutan - 2 - one oxime in accordance with Examples 2 and 3.

Example 10.

Preparation of N,1 - dimethyl - 3 - (4 - bromophenyl) - 3 - phenylpropylamine.

The free base of 3 - (4 - bromophenyl) - 1 - methyl - 3 - phenylpropyl - amine (0.70 g, 0.0023 mol) was dissolved in 50 ml of chloroform, 1.2 ml (0.0024 mol) of 2 M NaOH and 0.25 g (0.0024 mol) of ethyl chloroformate were added separately and dropwise with vigorous stirring at 15° C. Stirring was continued for 2 h at room temperature.

Then 25 ml of water was added and the organic layer was separated, dried, and the solvent was evaporated to give 1.0 g of N-ethoxycarbonyl - 3 - (4 - bromophenyl)-1 - methyl - 3 - phenylpropyl - amine as a colourless oil.

Treatment of the carbamate with 0.25 g (0.006 mol) of $LiAlH_4$ in 60 ml of ether for 14 h gave 0.20 g of the secondary amine after extraction with ether/hydrochloride and NaOH/ether. The hydrochloride was prepared and recrystallized from 18 ml of acetone to give 0.12 g, mp 146—148° C.

The oxalate had mp 106—111° C from acetone.

Example 11.

Preparation of 3 - (3 - bromophenyl) - 1 - methyl - 3 - phenylpropylamine (Method d).

A mixture of 22.1 g (0.073 mol) of 4 - (3 - bromophenyl) - 4 - phenylbutan-2 - one and 230 ml of formamide was heated for 8 h at 180° C. After cooling water was added and the product was taken up in ether. Drying and evaporation of the solvent gave 30.5 g of a residue.

To this residue 85 ml of conc. hydrochloric acid was added and the mixture was heated under refluxing conditions for 3 h. Water was added and the non basic materials were removed by shaking the reaction mixture with 100 ml of ether. The aqueous layer was separated and made alkaline by addition of 120 ml of 10 M NaOH. Extraction with 3 × 200 ml of ether, drying (Na_2SO_4) and evaporation of the solvent gave 12.9 g of the desired amine.

The maleate was prepared by addition of a hot ethanolic solution of 4.9 g of maleic acid int a warm sclution cf the amine in 100 ml of ethyl acetate. Recrystallization from EtOH—EtOAc gave 8.4 g of the maleate, mp 158—161° C.

Analysis: C calcd 57.2%, found 57.5%, H calcd 5.28%, found 5.35%, Br calcd 19.0%, found 19.1%, N calcd 3.33%, found 3.20%, 0 calcd 15.2%, found 15.0%.

Example 12.

Preparation of 3,3 - di - (4 - fluorophenyl) - 1 - methyl - propylamine hydrochloride (Method c).

3,3 - di - (4 - flucrophenyl) - 1 - methyallylamine (0.9 g, 0.003 mol) was dissolved in 100 ml of ethanol and transferred to a Parr hydrogenation flask. 1.0 ml of concentrated hydrochloric acid was added followed by 0.2 g of 5% palladium on charcoal. The hydrogenation was effected at a pressure of 3.9 atm for 5.5 h. The reaction mixture was filtered to remove the catalyst and the solvent of the filtrate was evaporated. Crystallization from EtOAc-i-Pr_2O gave 0.75 g of the desired product, m.p. 225—229° C.

Analysis: C calcd 64.5%, found 64.5%, H calcd 6.09%, found 6.11%, Cl calcd 11.9%, found 11.8%, F calcd 12.8%, found 12.7%, N calcd 4.70%, found 4.55%.

By the same method there were prepared from the appropriate allylamines:

Example 13.

By the method of Example 12,3,3 - di - (4 - methoxyphenyl) - 1 - methylpropylamine fumarate, mp 153—157°C, (EtOH-i-Pr_2O) was prepared from the corresponding allylamine.

Example 14.

By the method of Example 12, 1,3',3" - trimethyl - 3,3 - diphenylpropylamine oxalate, mp 214—215° C (EtOH—EtOAc) was prepared from the corresponding allylamine.

Example 15.

Preparation of 4,4 - di - (4 - bromophenyl) - 4 - hydroxy - 2 - butylamine oxalate.

A solution of 81.5 g (0.35 mol) 1,4 - dibromobenzene in 500 ml of diethyl ether was added to a stirred mixture of 8.3 g (0.35 mol) magnesium turnings in 25 ml diethyl ether at such a rate that reflux was maintained. After an additional stirring for 1.5 h at room temperature the mixture was cooled in an ice-bath and a solution of 11.3 g (0.11 mol) of ethyl 3 - aminobutyrate in 25 ml diethyl ether was added during 15 min.

The mixture was stirred for 1.25 h at ice-cooling and then for 2.5 h at reflux. An aqueous cold solution of 25 g ammonium chloride was slowly added, and after stirring the mixture was extracted twice with ether. The ethereal layer was dried over sodium sulphate and the amine was precipitated (10.9 g, 20% yield) with oxalic acid dissolved in ether. M.p. 191—194° C.

Elemental analysis: $C_{18}H_{19}Br_2NO_5$: Found C 44.5, H 4.0, N 2.7 and D 16.8%. Calculated: C 44.20, H 3.91, N 2.86 and O 16.35%.

Example 16.

Preparation of 3 - amino - 1,1 - di(4 - bromophenyl) - 1 - butene hydrochloride (method e).

A solution of 3.8 g 4,4 - di(4 - bromophenyl) - 4 - hydroxy - 2 - butylamine oxalate, 25 ml acetic acid and 5 ml conc. aqueous hydrogen chloride was heated under reflux for 30 min. The solvent was evaporated and the residue was made alkaline with sodium hydroxide and extracted twice with ether. The ethereal layer was dried over sodium sulphate and the solvent was evaporated. Acetonitrile and hydrogen chloride in ether were added and the hydrochloride of the title compound (1.7 g) was obtained after recrystallization from acetonitrile/ether. M.p. 216—220° C.

Elemental analysis: $C_{16}H_{16}Br_2ClN$. Found: C 46.7, H 3.9, Cl 8.8 and N 3.1%. Calculated: C 46.02, H 3.86, Cl 8.49 and N 3.35%.

Example 17.

Preparation of 3 - amino - 1,1 - di(4 - methoxyphenyl) - 1 - butene fumarate (method e).

A solution of 58.0 g (0.31 mol) of 4-bromoanisole in 300 ml diethyl ether was added dropwise to a stirred mixture of 7.78 g (0.32 mol) magnesium turnings in 250 ml of diethyl ether during 2 h. The mixture was stirred at room temperature for another 1.5 h and then heated under reflux for 1.5 h. The mixture was cooled in an ice-bath and a solution of 10.3 g (0.10 mol) ethyl 3 - aminobutyrate in 25 ml diethyl

ether was added during 20 min. After stirring over-night at room temperature an aqueous solution of 16.6 g (0.31 mol) ammonium chloride was slowly added. The mixture was stirred and then made alkaline and filtered. After separation of the ether phase the aqueous phase was extracted with ether. The combined ethereal layers were extracted twice with 2 M hydrogen chloride. The aqueous phase was made alkaline and extracted with ether and dried over sodium sulphate. After evaporation of the solvent 10.1 g of yellow oil was obtained, which was dissolved in 75 ml of acetic acid and 15 ml of conc. aqueous hydrogen chloride.

The solution was heated under reflux for 30 min and then the solvent was evaporated. The residue was made alkaline and extracted with ether. The ethereal layer was washed with water and extracted with 0.5 M hydrogen chloride. The aqueous phase was washed with ether, made alkaline and extracted with ether. After drying over sodium sulphate the ether was evaporated to give 5.9 g of the title compound as an oil in 21% yield.

The amine was converted to the fumarate, which was recrystallized twice from ethanol/ethyl acetate/hexane to give 6.2 g (17% yield) of the fumaric acid salt in the form $C_{18}H_{21}NO_3 \cdot 3/4C_4H_4O_4$. M.p. 167—167.5° C.

Elemental analysis: $C_{21}H_{24}NO_5$: Found C 67.8, H 6.52, N 3.89 and O 21.5%. Calculated: C 68.09, H 6.53, N 3.78 and O 21.60%.

Example 18.

3 - amino - 1,1 - di - (4 - fluorophenyl) - 1 - butene fumarate was prepared according to Example 17. M.p. 225—231° C.

Example 19.

3 - amino - 1,1 - di - (3 - methylphenyl) - 1 - butene hydrochloride was prepared according to Example 17. M.p. 216—217.5° C.

Example 20.

Preparation of 1 - (4 - bromophenyl) - 1 - phenyl - butene.

Sodium dimethylsulfoxide in DMSO, prepared by heating 3.8 g (0.08 mol) sodium hydride (50% in oil) in 100 ml dimethyl sulfoxide at 80° C for 40 min, was mixed with 27.0 g (0.07 mol) propyltriphenylphosphonium bromide, prepared by heating propylbromide and triphenylphosphine in toluene at reflux temperature for 14 h. The mixture was stirred under nitrogen atmosphere at room temperature for 1.5 h. Then a solution of 13.1 g (0.05 mol) of 4 - bromobenzophenone, in a mixture of 100 ml dimethylsulfoxide and 100 ml of anhydrous tetrahydrofuran was added at room temperature. The reaction mixture was stirred for 2 h, then it was poured into 1.000 ml of ice-water. The product was extracted with 3 × 300 ml of ether, the combined ethereal layer was washed with 100 ml of water. Drying (Na_2SO_4) and evaporation of the solvent gave 18 g of oily residue. After trituration with 100 ml of diisopropyl-ether crystals of triphenylphosphinoxide was separated by filtration. Distillation of the filtrate at 4 Pa gave 12.2 g of 1 - (4 - bromophenyl) - 1 - phenyl - butene, b.p. 120—130° C. Yield 85%.

Example 21.

Preparation of 3 - (4 - bromophenyl) - 3 - phenyl - 1 - methylallylbromide.

To a solution of 22.6 g (0.0787 mol) of 1 - (4 - bromophenyl) - 1 -phenyl-butene in 800 ml of carbon tetrachloride 14.0 g (0.0787 mol) of N-bromosuccinimide was added. The mixture was heated to reflux temperature after the addition of 0.7 g of alpha, alpha-azabis-butyronitrile. After 3.5 h all NBS had been consumed and the reaction mixture was cooled and filtered. 7.8 g of succinimide was separated and the volume of the filtrate was reduced to 50 ml by evaporation at 35° C. TLC of a sample on silica in diiscpropyl ether hexane (1:1) showed a new spot at Rf 0.62 (the starting olefin had Rf 0.55). The material was used without further isolation or purification due to its high reactivity with nucleophilic agents.

Example 22.

Preparation of 3 - (N - phthalimido) - 1 - (4 - bromophenyl) - 1 - phenylbutene (method f).

A solution of crude 3 - (4 - bromophenyl) - 3 - phenyl - 1 - methylallylbromide (29 g, 0.08 mol) in 50 ml carbon tetrachloride was mixed with 15.0 g (0.08 mol) of N - potassiumphthalimide and 120 ml of anhydrous dimethylformamide. The mixture was stirred at 50° C for 14 hours.

Dilution with water (excess) and extraction of the product with diethylether gave 18 g of an oil after drying and evaporation of the solvent. Column chromatography on silica with diisopropyl ether as the eluent afforded the geometrical isomers: 2.6 g of the (Z)-form, $R_f = 0.30$, and 3.7 g of the (E)-form, $R_f = 0.26$ in diisopropyl-etherhexane (1:1).

Example 23.

Preparation of (Z) - 3 - amino - 1 - (4 - bromophenyl) - 1 - phenylbutene maleate.

To a stirred solution of 0.43 g (0.001 mol) of (Z) - 3 - phthalimido - 1 - (4-bromophenyl) - 1 - phenylbutene in 30 ml of methanol 0.25 g (0.005 mol) of hydrazine hydrate was added at room temperature. In order to dissolve all the phthalimide 10 ml of carbon tetrachloride was added. The mixture was stirred and heated at 60° C for 2 h. After cooling the solvent was removed *in vacuo* and the residue was taken up in ether. The product was extracted with 3 × 50 ml of 0.5 M HCl, the combined aqueous layer was made alkaline with 10 M NaOH and extracted with 2 × 50 ml of ether. Drying and evaporation of the solvent gave 0.23 g of the title compound as an oil. The maleate had m.p. 174—176° C from ethanol. The UV spectrum in ethanol had λmax 237 nm.

Elemental analysis: $C_{20}H_{20}BrNO_4$. Found: C 57.1, H 4.80, Br 20.3, N 3.10 and O 15.2%. Calculated: C 57.43, H 4.82, Br 19.10, N 3.35 and O 15.30%.

Example 24.

(E) - 3 - amino - 1 - (4 - bromophenyl) - 1 - phenylbutene oxalate was prepared from the corresponding phthalimide according to Example 23. M.p. 145—148° C.

Example 25.

Preparation of (Z) - 3 - amino - 1 - (3 - bromophenyl) - 1 - phenylbut - 1 - ene maleate (method f).

To a stirred solution of 0.43 g (0.001 mol) of (Z) - 3 - phthalimido - 1 - (3-bromophenyl) - phenylbutene in 40 ml of methanol 0.35 g (0.007 mol) of hydrazine hydrate was added at room temperature. The mixture was heated under reflux for 2.5 h. The solvent was evaporated and the residue was taken up in ether. Extraction with 3 × 25 ml of 0.5 M HCl followed by alkalization of the combined aqueous layer with 10 M NaOH and extraction with 2 × 50 ml of ether gave 0.19 g of residue after drying and evaporation of the solvent. The maleate was prepared from 15 ml ethyl acetate-ethanol (2:1) to give 0.12 g (28%). M.p. 198—200° C.

Elemental analysis: $C_{20}H_{20}BrNO_4$. Found: C 56.3, H 4.7, and N 3.2%. Calculated C 57.43, H 4.82 and N 3.35%.

Example 26.

(E) - 3 - amino - 1 - (3 - bromophenyl) - 1 - phenylbutene hydrochloride was prepared from the corresponding phthalimide according to Example 25. M.p. 118—123° C.

Example 27.

(Z - 3 - amino - 1 - (4 - bromophenyl) - 1 - (3 - pyridyl) - butene oxalate was prepared from the corresponding phthalimide according to Example 25.

Example 28.

Preparation of 3 - (N - Phthalimido - 1 - (4 - bromophenyl) - 1 - phenylbutene.

3 - (4 - bromophenyl) - 1 - methyl - 3 - phenylpropylamine as the free base (41.2 g, 0.136 mol) was dissolved in 350 ml of acetic acid. Phthalic anhydride (20.0 g, 0.136 mol) was added and the mixture was heated with stirring under reflux (bath temperature 120° C) for 2 h. After cooling the solvent was evaporated *in vacuo*. The residue was shaken with a mixture of 800 ml of ether and 500 ml of 2 M NaOH. The ethereal layer was separated and washed with 100 ml 1 M hydrochloric acid. Drying and evaporation gave 49.5 g of a tan oil. Thin layer chromatography on silica in diisopropylether showed one spot of Rf 0.42. NMR showed a four proton multiplet at 7.7 ppm from TMS, characteristic of phthalimides. The material was used without further purification. Yield 83%.

Example 29.

Preparation of 3 - (N - phthalimido) - 1 - (4 - bromophenyl) - 1 - phenylbut - 1-ene (method g).

T a stirred solution of 24.6 g (0.057 mol) 3 - (N - phthalimido) - 1 - (4-bromophenyl) - 1 - phenylbutane in 40 ml of carbon tetrachloride 10.0 g (0.057 mol) of N - bromosuccinimide was added. The mixture was stirred and 0.5 g of alpha, alpha-azaisobutyronitrile was added as radical initiator. Stirring was continued under reflux temperature for 2.5 h. The reaction mixture was cooled and filtered. Upon evaporation of the solvent 32.4 g of a residue was obtained. NMR of a sample in $COCl_3$ showed a double quartet at 5.0 ppm from TMS and a doublet at 6.6 ppm. TLC on silica in diisopropyl ether showed a spot with Rf 0.28, identical with the Rf-value of the material prepared according to Example 22.

The following Examples illustrate how the compounds of the present invention may be included in pharmaceutical preparations.

Example 30.

Preparation of soft gelatin capsules.

500 g of active substance were mixed with 500 g of corn oil, whereupon the mixture was filled in soft gelatin capsules, each capsule containing 100 mg of the mixture (i.e. 50 mg of active substance).

Example 31.

Preparation of soft gelatin capsules.

500 g of active substance were mixed with 750 g of peanut oil, whereupon the mixture was filled in soft gelatin capsules, each capsule containing 125 mg of the mixture (i.e. 50 mg of active substance).

Example 32.

Preparation of tablets.

50 kg of active substance were mixed with 20 kg of silicic acid of the trade mark Aerosil. 45 kg of potato starch and 50 kg of lactose were mixed therewith and the mixture was moistened with a starch paste prepared from 5 kg of potato starch and distilled water, whereupon the mixture was granulated through a sieve. The granulate was dried and sieved, whereupon 2 kg of magnesium stearate was mixed into it. Finally the mixture was pressed into tablets each weighing 172 mg.

Example 33.

Preparation of an emulsion.

100 g of active substance were dissolved in 2500 g of peanut oil. From the solution thus obtained, 90 g of gum arabic, aroma and colouring agents (q.s.) and 2500 g of water an emulsion was prepared.

Example 34.

Preparation of a syrup.

100 g of active substance were dissolved in 300 g of 95% ethanol, whereupon 300 g of glycerol, aroma and colouring agents (q.s.) and 1000 ml of water were mixed therein. A syrup was obtained.

Example 35.

Preparation of a solution.

100 g of active substance were dissolved in 2000 g of polyoxyethylene sorbitan monooleate, whereupon flavouring agents and colouring agents (q.s.) and water to 5000 ml was mixed therein. A drop solution was obtained.

Example 36.

Preparation of effervescing tablets.

100 g of active substance, 140 g of finely divided citric acid, 100 g of finely divided sodium hydrogen carbonate, 3.5 g of magnesium stearate and flavouring agents (q.s.) were mixed and the mixture was pressed into tablets each containing 100 mg of active substance.

Example 37.

Preparation of a drop solution.

100 g of active substance were mixed with 300 g of ethanol, whereupon 300 g

of glycerol, water to 1000 ml, aroma and flavouring agents (q.s.) and 0.1 N sodium hydroxid solution (to pH 4.5 to 5.5) was added while stirring. A drops solution was obtained.

Example 38.

Preparation of a sustained release tablet.

200 g of active substance were melted together with 50 g of stearic acid and 50 g of carnauba wax. The mixture thus obtained was cooled and ground to a particle size of at most 1 mm in diameter. The mixture thus obtained was mixed with 5 g of magnesium stearate and pressed into tablets each weighing 305 mg. Each tablet thus contains 200 mg of active substance.

Pharmacological evaluation.

Depressions are considered to be connected with changes in the biochemical processes of the brain which processes control the mood. The nature of these biochemical processes are largely unknown but in depressive states there is evidence for a decreased activity of monoaminergic brain neurons. The monoamines, noradrenaline (NA), dopamine (DA) and 5 - hydroxytryptamine (5—HT), are of great interest in this respect.

It has been demonstrated that NA, DA and 5—HT is localised in three different types of neurons and may function as transmittors in the central nervous system. The moncamines are stored in special structures, granules, situated in enlargements of the nerve endings, varicosities. The varicosity is separated from the effector neuron by a space, the synaptic cleft or spatium. As a result of a nerve stimulation the transmittor is released from the granule into the synaptic cleft and reaches the receptor of the effector neuron and generates a nerve impulse. After impulse generation the amines are inactivated by mainly two mechanisms: a re-uptake mechanism at the cell membrane and enzymatic conversion by catechol-O-methyltransferase to form methylated metabolites. There is also an inactivating enzyme within the varicosities, monoamine oxidase (MAO), that is stored in the mitochondria and inactivates the amines intracellularly.

When MAO-inhibitors are administered, an increased amount of transmittor substance becomes available for release at the nerve ending.

Another way of increasing the amine levels at the receptor is exerted by the tricycle antidepressants. It has been shown that this type of compounds inhibits the re-uptake mechanism of NA and 5—HT, and the antidepressive action is assumed to be related to the uptake inhibition of NA and 5—HT.

It has been proposed, that some depressions are caused by deficiency in either one of the neurotransmittors and some of deficiency in both.

An antidepressant effect should thus be obtained with compounds which are able to inhibit the re-uptake of one or both NA and 5—HT.

Pharmacological methods.

The test method described in Europ. J. Pharmacol. 17, 107, 1972. This method involves the measurement of the decrease in the uptake of ^{14}C—5-hydroxytrpytamine (^{14}C—5—HT) and ^{3}H-noradrenaline (^{3}H—NA) in brain slices from mice after *in vivo* and *in vitro* administration of the test substance.

Inhibition of the uptake of ^{14}C—5—HT and ^{3}H—NA *in vitro* and *in vivo*.

The test substances were administered intraperitoneally half an hour before the animals were killed. The midbrain was take out, sliced and incubated in a mixture consisting of 0.2 nmole of ^{14}C—5—HT, 0.2 nmole of ^{3}H—NA and 11 µmole of glucose in 2 ml of Krebs Henseleit-buffer, pH 7.4, per 100 mg of brain slices. The incubation time was 5 minutes with 5 minutes of preincubation before the labelled amines were added. The slices were dissolved in Soluene and the amounts of radioactive amines taken up were determined by liquid scintillation. The doses producing 50 per cent decrease of the active uptake (ED_{50}) of ^{14}C—5—HT and ^{3}H—NA were determined graphically from dose response curves. Active uptake is defined as that part of the radioactive uptake which is inhibited by a high concentration of cocaine.

In the *vitro* administration method slices of mouse midbrain were preincubated for 5 minutes with solution of the compound to be tested and then incubated as described above. The concentration producing 50 per cent inhibition of the active uptake IC_{50} of ^{14}C—5HT and ^{3}H—NA was determined graphically from dose response curves.

The test results are given in Table I.

TABLE I

Inhibition of neuronal uptake of 5-hydroxytryptamine and noradrenaline in slices from mouse brain

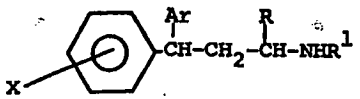
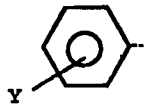
Compound								Inhibition of the uptake *in vitro* IC_{50} (μM)		Inhibition of the uptake *in vivo* i.p. ED_{50} (μmole/kg)	
								NA	5–HT	NA	5–HT
	Ar	Y	X	R	R^1	isomer	salt				
Code											
CPK 163	,,	4-F	H	CH_3	H	α	Ox	0.54	0.28	32	32
CPK 170	,,	4-F	H	CH_3	H	β	HCl	0.25	0.18	34	37
CPK 185	,,	2-Br	H	CH_3	H	α	Mal	0.36	2.24	4.1	5.7
CPK 197	,,	2-Br	H	CH_3	H	β	Mal	0.24	0.50	28	>95
CPK 155	,,	3-Br	H	CH_3	H	α	Mal	2.0	0.8	49	>95
CPK 184	,,	3-Br	H	CH_3	H	β	Mal	0.31	0.11	7.7	9.9
CPK 165	,,	4-Br	H	CH_3	H	α	Mal	0.95	0.62	62	61
CPK 171	,,	4-Br	H	CH_3	H	β	Mal	0.21	0.14	29	29
CPK 187	,,	4-Br	H	CH_3	CH_3	α + β	Ox	8.00	0.71	>98	98
CPK 195	,,	4-CF_3	H	CH_3	H	α	Mal	4.0	2.7	>98	98
CPK 199	,,	4-CF_3	H	CH_3	H	β	Mal	2.25	0.76	>98	>98

TABLE I (Continued)

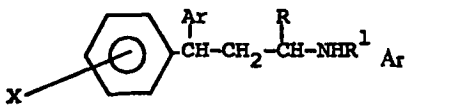
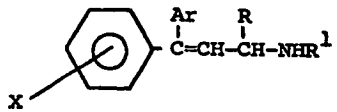
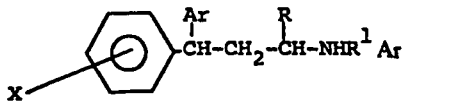
Compound								Inhibition of the uptake *in vitro* IC_{50} (μm)		Inhibition of the uptake *in vivo* i.p. ED_{50} (μmole /kg)	
								NA	5–HT	NA	5–HT
		Y	X	R	R^1	isomer	salt**				
Code											
CPK 180		4-CH_3O	H	CH_3	H	α	Mal	0.51	0.30	78	54
CPK 198	,,	4-CH_3O	H	CH_3	H	β	Mal	0.83	0.16	52	33
FLA 615	,,	4-F	4-F	CH_3	H	–		1.9	0.30	57	29
FLA 619	,,	3-CH_3	3-CH_3	CH_3	H	–		0.8	0.7	48	116
FLA 614	,,	4-CH_3O	4-CH_3O	CH_3	H	–		0.80	0.15	100	25
											
FLA 608	,,	4-Br	4-Br	CH_3	H	–	HCl	4.8	2.5	57	62
FLA 611	,,	4-OCH_3	4-OCH_3	CH_3	H	–	Fum	1.7	0.4	108	63
FLA 613	,,	4-F	4-F	CH_3	H	–	Fum	1.5	0.3	106	38
FLA 618	,,	3-CH_3	3-CH_3	CH_3	H	–	HCl	2.4	1.3	56	93
CPK 150	,,	4-Br	H	CH_3	H	Z*	Mal	2.0	3.0	96	>96

TABLE I (Continued)

Compound								Inhibition of the uptake *in vitro* Ic_{50} (μM)		Inhibition of the uptake *in vivo* i.p. ED_{50} (μmole/kg)	
								NA	5–HT	NA	5–HT
		Y	X	R	R^1	isomer	salt				
Code											
CPK 204		4-Br	H	CH_3	H	E*	Ox	2.6	0.6	48	40
CPK 217	,,	3-Br	H	CH_3	H	Z*	Mal	1.1	0.6	35	118
CPK 215	,,	3-Br	H	CH_3	H	E*	HCl	1.3	0.7	24	96
CPP 179	3-pyridyl		4-Br	CH_3	H	Z*	Ox	1.6	0.2	>89	89
Prior art compounds											
3,3-diphenyl-1-methylpropylamine fumarate								0.50	0.50	50	75
N-methyl-3-(4-bromophenyl)-3-(3-pyridyl)-allylamine		E-isomer						0.8	2.5	25	102
	,,	Z-isomer						1.5	0.10	>102	19
Chloroimipramine								0.9	0.09	150	20
Bromfeniramine								3.8	0.2	50	10

* Geometrical isomerism

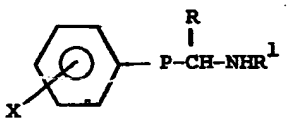
** HCl = hydrochloride
Mal = maleate
Ox = oxalate
Fum = fumarate

The pharmaceutical tests show that the compounds are able to inhibit the uptake of noradrenaline and 5-hydroxytryptamine. A pronounced non-selective activity is shown for the compounds having codes CPK 170, CPK 171, CPK 180 and CPK 184. A pronounced selective activity on uptake of noradrenaline is seen in compounds CPK 185, CPK 215 and CPK 217 while a pronounced selective activity on uptake of 5-hydroxytryptamine is seen in compounds FLA 611, FLA 615, CPK 198 and CPK 204.

A strong non-selective activity is considered to be especially advantageous, as compounds having such activity may be employed in the treatment of depressions in which the neurotransmittor deficiency is unknown as well as in those cases wherein it is established that the deficiency pertains to both noradrenaline and 5-hydroxytryptamine.

WHAT WE CLAIM IS:—

1. A compound of the general formula



(I)

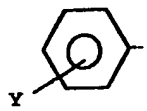
wherein P represents

or

in which Ar represents the group

wherein Y is bound in the 2-, 3- or 4-position and represents a C_1—C_3 alkyl or alkoxy group, halogen, a trifluoromethyl group or an amino or mono- or di-C_1—C_3 alkylamino group, or Ar represents a pyridyl group bound in the 2-, 3- or 4-position, X represents hydrogen or, when Ar represents a pyridyl group, X can also represent a C_1—C_3 alkyl or alkoxy group, halogen a trifluoromethyl group or an amino or mono- or di-C_1—C_3 alkylamino group, R represents a C_1—C_3 alkyl group and R^1 represents hydrogen or a C_1—C_3 alkyl group; or a pharmaceutically acceptable, anhydrous or hydrated, acid addition salt thereof.

2. A compound according to claim 1 wherein Ar represents the group



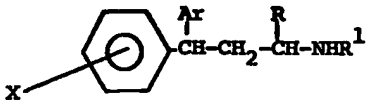
wherein Y is as defined in claim 1.

3. A compound according to claim 2 wherein Y represents F, Br or CH_3O—.

4. A compound according to any one of the preceding claims wherein R is a methyl group.

5. A compound according to any one of the preceding claims wherein R^1 is hydrogen.

6. A compound of the general formula

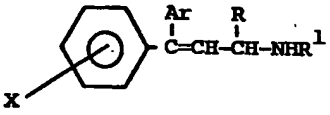


(Ia)

wherein Ar, X, R and R^1 are as defined in any one of claims 1 to 5, or a pharmaceutically acceptable, anhydrous or hydrated, acid addition salt thereof.

7. A compound according to claim 6 wherein Ar, X, R and R^1 are as defined in any one of claims 1 to 5 but, when Ar represents pyridyl, X does not represent hydrogen.

8. A compound of the general formula



Ib

wherein Ar, X, R and R^1 are as defined in any one of claims 1 to 5, or a pharmaceutically acceptable, anhydrous or hydrated, acid addition salt thereof.

9. A compound according to claim 6 in the form of a pure diastereomer.

10. A compound according to claim 7 in the form of a pure diastereomer.

11. A compound according to claim 8 in the form of a pure geometrical isomer.

12. A compound according to claim 6 in the form of a pure optical enantiomer.

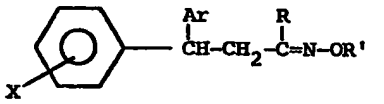
13. A compound according to claim 7 in the form of a pure optical enantiomer.

14. A compound according to claim 8 in the form of a pure optical enantiomer.

15. (β)-3-(4-fluorophenyl)-1-methyl-3-phenylpropylamine,
(β)-3-(4-bromophenyl)-1-methyl-3-phenylpropylamine,
(α)-3-(4-methoxyphenyl)-1-methyl-3-phenylpropylamine,
(β)-3-(3-bromophenyl)-1-methyl-3-phenylpropylamine,
(α)-3-(2-bromophenyl)-1-methyl-3-phenylpropylamine or
(β)-3-(4-methoxyphenyl)-1-methyl-3-phenylpropylamine,
or a pharmaceutically acceptable, anhydrous or hydrated acid addition salt of any of these compounds.

16. (E)-3-amino-1-(3-bromophenyl)-1-phenylbutene,
(Z)-3-amino-1-(3-bromophenyl)-1-phenylbutene or
(E)-3-amino-1-(4-bromophenyl)-1-phenylbutene,
or a pharmaceutically acceptable, anhydrous or hydrated acid addition salt of any of these compounds.

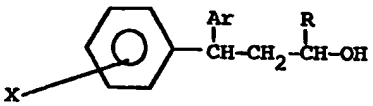
17. A process for preparing a compound of the general formula Ia as defined in claim 6 wherein R^1 is hydrogen, which comprises reducing a compound of the formula



II

wherein Ar, X and R are as defined in claim 6 and R′ is a hydrogen atom or an alkyl, acyl or alkylsulfonyl group having 1—3 carbon atoms, to obtain a compound of formula Ia, in which R^1 is hydrogen.

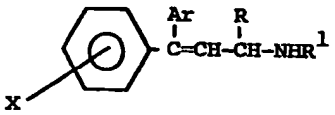
18. A process for preparing a compound of formula Ia as defined in claim 6 which comprises preparing a reactive ester of an alcohol of the formula



III

wherein Ar, X and R are as defined in claim 6, and reacting the ester obtained with an amine of the formula NH_2R^1, wherein R^1 is as defined in claim 6.

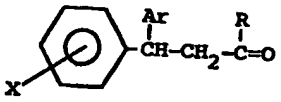
19. A process for preparing a compound of formula Ia as defined in claim 6 which process comprises reducing a compound of the formula



Ib

wherein Ar, X, R and R^1 are as defined in claim 6.

20. A process for preparing a compound of formula Ia as defined in claim 6 wherein R^1 is hydrogen or methyl, which comprises reacting a ketone of the formula

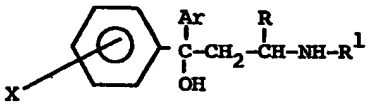


IV

wherein Ar, X and R are as defined in claim 6, with ammonium formate or methylammonium formate according to Leuckart-Wallach, to obtain a compound of formula Ia in which R^1 is hydrogen or methyl.

21. A process according to any one of claims 17 to 20 wherein the compound of formula Ia is as defined in claim 7.

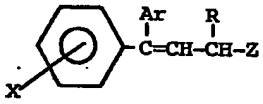
22. A process for preparing a compound of formula Ib as defined in claim 8 which comprises dehydrating a carbinol of the formula



VII

wherein Ar, X, R and R^1 are as defined in claim 8.

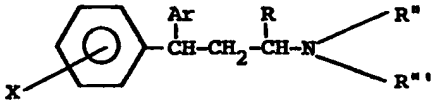
23. A process for preparing a compound of formula Ib as defined in claim 8 which comprises reacting a compound of the formula



VIII

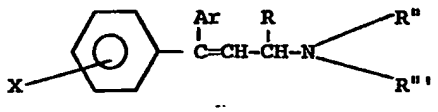
wherein Ar, X and R are as defined in claim 8 and Z is a leaving group, with an amine of the formula NH_2R^1 or a derivative thereof, which preparation further involves conversion of an amine derivative when a derivative of an amine of the formula NH_2R^1 is employed.

24. A process for preparing a compound of formula Ib as defined in claim 8 wherein R^1 is hydrogen which comprises oxidising the benzylic carbon atom of a compound of the formula



IX

wherein Ar, X and R are as defined in claim 8 and R″ and R‴ are protecting groups for the amino function, followed by elimination of the group formed by oxidation at the benzyl carbon atom to provide a compound of the formula



X

which is transformed into the compound of formula Ib where R^1 is hydrogen, by removing groups R″ and R‴.

25. A process according to any one of claims 17 to 20 wherein the product is a primary amine which is subsequently converted to the corresponding methyl-amine by methylation.

26. A process according to claim 21 where the product is a primary amine which is subsequently converted to the corresponding methyl-amine by methylation.

27. A process according to claims 22 to 24 where the product is a primary amine which is subsequently converted to the corresponding methyl-amine by methylation.

28. A process according to any one of claims 17 to 20 where the compound prepared is subsequently converted into a pharmaceutically acceptable, anhydrous or hydrated acid addition salt thereof.

29. A process according to claim 21 where the compound prepared is subsequently converted into a pharmaceutically acceptable, anhydrous or hydrated acid addition salt thereof.

30. A process according to any one of claims 22 to 24 where the compound prepared is subsequently converted into a pharmaceutically acceptable, anhydrous or hydrated acid addition salt thereof.

31. A process for preparing a compound of formula Ia or salt thereof as defined in claim 7 substantially as hereinbefore described with reference to any one of Examples 2 to 7 and 9 to 11.

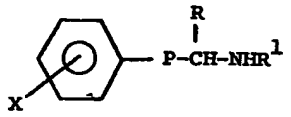
32. A process for preparing a compound of formula Ib or salt thereof as defined in claim 8 substantially as hereinbefore described with reference to any one of Examples 23 to 27.

33. A compound of formula I or salt thereof as claimed in any one of claims 1 to 16 when prepared by a process as claimed in any one of claims 17 to 32.

34. A compound of formula Ia or salt thereof as claimed in claim 7, 10 or 13 when prepared by a process as claimed in any one of claims 21, 26, 29 and 31.

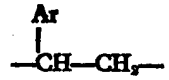
35. A compound of formula Ib or salt thereof as claimed in claim 8, 11, or 14 when prepared by a process as claimed in any one of claims 22 to 24, 27, 30 and 32.

36. A pharmaceutical preparation which comprises as active ingredient, in association with a pharmaceutically acceptable carrier, a therapeutically effective amount of a compound of the general formula



(I)

wherein P represents

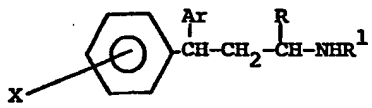


or

in which Ar represents the group

where Y is bound in the 2-, 3- or 4-position and represents a C_1—C_3 alkyl or alkoxy group, halogen, a trifluoromethyl group or an amino or mono- or di-C_1—C_3 alkylamino group, or Ar represents a pyridyl group bound in the 2-, 3- or 4-position, X is bound in the 2-, 3- or 4-position and represents hydrogen, a C_1—C_3 alkyl or alkoxy group, halogen, a trifluoromethyl group or an amino or mono- or di-C_1—C_3 alkylamino group, R represents a C_1—C_3 alkyl group and R^1 represents hydrogen or a C_1—C_3 alkyl group; or a pharmaceutically acceptable, anhydrous or hydrated, acid addition salt thereof.

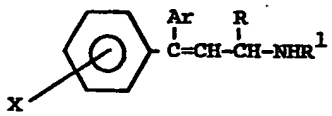
37. A preparation according to claim 36 wherein the active ingredient is a compound of the general formula



Ia

wherein Ar, X, R and R^1 are as defined in claim 36 with the proviso that when Ar represents pyridyl, X does not represent hydrogen, or a pharmaceutically acceptable, anhydrous or hydrated, acid addition salt thereof.

38. A preparation according to claim 36 wherein the active ingredient is a compound of the general formula



Ib

wherein Ar, X, R and R^1 are as defined in claim 36, or a pharmaceutically acceptable, anhydrous or hydrated, acid addition salt thereof.

39. A preparation according to claim 36 substantially as hereinbefore described with reference to any one of Examples 30 to 38.

40. A method for the treatment of depression, which comprises administering to a non-human host suffering from depression a therapeutically acceptable amount of a compound of formula I or salt thereof as defined in any one of claims 36 to 38, or a preparation as claimed in any one of claims 36 to 39.

41 A method for the treatment of anxiety, which comprises administering to a non-human host suffering from anxiety a therapeutically acceptable amount of a compound of formula I or salt thereof as defined in any one of claims 36 to 38, or a preparation as claimed in any one of claims 36 to 39.

42. A method according to claim 40 or 41 wherein a compound of formula Ia or salt thereof as defined in claim 37 or a preparation as claimed in claim 37 is administered.

43. A method according to claim 40 or 41 wherein a compound of formula Ib or salt thereof as defined in claim 38 or a preparation as claimed in claim 38 is administered.

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